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PATENT SPECIFICATION

DRAWINGS ATTACHED

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COMPLETE SPECIFICATION

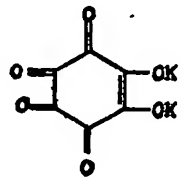
Dipotassium Rhodizonate and the production thereof

We, SHIONOGI & CO. LTD., a Japanese Body Corporate of 12, 3-chome, Doshomachi, Higashi-ku, Osaka, Japan, and IATROCHEMICAL INSTITUTE OF THE PHARMACOLOGICAL RESEARCH FOUNDATION, a Japanese Body Corporate of 2—963 Daita, Setagaya-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to dipotassium rhodizonate and production thereof.

It is an object of the present invention to embody dipotassium rhodizonate as an antidiabetic agent. Another object of this invention is to embody an improved process for preparing dipotassium rhodizonate. These and other objects will be apparent, to those conversant with the art to which the present invention pertains, from the subsequent description.

The said dipotassium rhodizonate is represented by the following formula



(I)

Rhodizonic acid and its salts are known compounds, and the known methods of synthesising them are represented as follows: (1) oxidation of inositol, hexahydroxybenzene or tetrahydroquinone; (2) reduction of triquinoyl; (3) polycondensation of glyoxal.

The first and second of the above three methods are not profitable for the mass production of rhodizonic acid because of expensiveness of the starting material and the difficulty of obtaining it on any industrial scale. The third method of polycondensing glyoxal is profitable for producing rhodizonic acid and its salts, since the starting glyoxal can be provided in large amounts and at low cost from the petrochemical industry.

As to the above third method, only polycondensing glyoxal in the presence of sodium sulfite and sodium carbonate to give sodium rhodizonate is known (U.S.S.R. Pat. No. 135,479). This method is a modification of the method of preparing tetrahydroquinone salt by condensation of glyoxal (Organic Syntheses, Vol. 42, p. 90—92 (1962)). However, in the said known method a large amount of tetrahydroxyquinone sodium salt is obtained as a byproduct besides the sodium rhodizonate in the reaction mixture owing to the solubility of sodium rhodizonate in water and the inappropriate hydrogen ion concentration of the reaction mixture. Separation and purification of the two products are difficult. Therefore, the said method is inappropriate as a process for preparing pure rhodizonic acid salt.

The present process for preparing dipotassium rhodizonate is an improvement of the said known method.

The present process comprises polycondensing glyoxal oxidatively in the presence of a potassium salt of carbonic acid and a potassium salt of sulfurous acid to prepare dipotassium rhodizonate. This process is effected ordinarily in an aqueous solvent at room temperature or while heating in aerial or oxygenic stream. At this time, the reaction mixture is kept at a hydrogen ion concentration (pH) of neutral to alkaline range, ordinarily 7.5 to 9.0, favourably 8.3 to 8.8. The terms "potassium salt of carbonic acid" and "potassium salt of sulfurous acid" are respectively intended to mean the salt generating potassium ions and carbonic ions and the salt generating potas-

sium ions and sulfurous ions. Examples of the former are potassium carbonate and potassium bicarbonate and of the latter, potassium sulfite and potassium bisulfite. In the present process both the salts are used in combination as the reagents.

These reagents serve not only for adjustment of the hydrogen ion concentration but also for controlling oxidative condensation by oxygen. For acceleration of the reaction rate, there may be favourably used a very small amount of potassium cyanide as a catalyst. In the present process the produced dipotassium rhodizonate can be easily recovered from the reaction mixture owing to its difficult solubility in water and easy solubility of other salts.

Dipotassium rhodizonate obtained in the present process is used, as is generally known, as a detecting reagent for a heavy metallic ion. By the studies of the present inventors, the present compound is found to be very useful as an antidiabetic drug.

Pure dipotassium rhodizonate obtained in the present invention and its derivatives (e.g. free acid, calcium salt, magnesium salt, organic base salt, etc.) show a blood sugar decreasing activity, that is, antidiabetic activity, as shown by insuline or mesoxalic acid, in biological and clinical tests. The biological and medical activities of the dipotassium salt obtained in the present process are illustratively shown as follows:

(I) Biological test

Blood sugar decreasing rate in mice two hours after the oral administration of dipotassium rhodizonate.

Dose (g/kg)	Number of test animals	Blood sugar decreasing rate (%)
3.1	5	—75
1.8	6	—80
1.0	8	—56
0.5	5	—32
0.3	6	—8
0.1	8	+14

(II) Clinical test

When 0.3 g of dipotassium rhodizonate is orally administered three times a day to a diabetic (man, 43 years old), the tendency of blood sugar value is represented by the Drawing attached hereto.

The toxicity of dipotassium rhodizonate by oral administration to mice (Lethal Dose 50) is over 6 g/kg. The present compound shows 100 times the anti-diabetic activity towards rabbits as does sodium mesoxalate, a known drug. The said pharmacological activity proves to be derived from the structure of rhodizonic acid itself and has no relation with the formation of salts.

The said dipotassium rhodizonate (I) may be administered alone or in combination with acceptable pharmaceutical carriers, the choice of which is determined by the preferred route of administration, the solubility of the substance and standard pharmaceutical practice. In general, the dosage of this substance is of approximately the same order of magnitude as the dosage of sodium mesoxalate, and the substance is useful in the treatment of the types of diabetic diseases often treated with the known anti-diabetic agent. Examples of pharmaceutical preparations are tablets, capsules, pills, suspension and solution. In the preparation of tablets, for example, these substances may be combined with binders such as gum tragacanth, acacia, corn starch and gelatin. It is also usually desirable to have present a disintegrating agent such as, for example, corn starch, potato starch or alginic acid. Also desirable usually is a lubricant such as stearic acid, magnesium stearate or talc along with a sweetening agent such as saccharin. Flavouring agents may be also used such as peppermint, oil of wintergreen or cherry flavour. In the preparation of capsules, fillers such as enumerated above for tablets can also be used. The compositions when used in the form of suspension or solution may be combined with an aqueous sugar or sorbitol type vehicle including a viscosity control agent such as Veegum (magnesium aluminium silicate), methyl cellulose or carboxymethylcelhulose and a suitable preservative such as sodium benzoate or parabens (methyl and propyl *p*-hydroxybenzoic acid salts). In these liquid preparations, colourings, flavourings and

buffers can also be included to produce a more pharmaceutically elegant preparation.

The compositions containing the dipotassium rhodizonate may be dispensed in dosage unit forms for a single daily therapeutic dose or in smaller units for multiple doses or in larger units for division into single doses. Parenteral compositions can also be dispensed in single units or in larger quantities from which single doses are withdrawn at the time of use.

Presently-preferred and practical embodiments of the present invention are illustratively shown in the following Examples. In these Examples, the relationship of parts by weight to parts by volume is the same as that between grams and milliliters. Temperatures are set forth in degrees centigrade.

EXAMPLE 1.

To distilled water (1380 parts by volume), there is added a newly prepared aqueous solution of glyoxal (40%) (345 parts by weight) at 60° C under stirring. The resultant mixture is made uniform at 60—62° C for 2 hours. After heating at 72° C once, the reaction mixture is chilled and adjusted to pH 5.6—5.8 with anhydrous potassium carbonate (18.4 parts by weight).

On the other hand, *potassium cyanide* (6 parts by weight) is added to a solution of potassium carbonate (390 parts by weight) and potassium sulfite (dihydrate) (291 parts by weight) in water (2000 parts by volume) and the resultant mixture warmed at 30° C.

To the said second solution, there is added dropwise the first solution at pH 8.3—8.8 in 1 hour. After finishing the dropping, the reaction mixture is stirred at 35° C for 30 minutes and allowed to stand overnight under ice-cooling. The precipitated dipotassium rhodizonate as purple-black fine crystals is collected by filtration from the reaction mixture, washed with 10% potassium acetate and cold ethanol and dried. This substance shows over 99.5% of purity after quantitative test.

EXAMPLE 2.

The reaction is effected as in Example 1 by using potassium bicarbonate and potassium sulfite dihydrate as the reagents for the second solution, and executed at pH 8.6 at 32—35° C. The product shows the same result of IR spectrum in comparison with pure dipotassium rhodizonate which is prepared from pure rhodizonic acid.

The following Examples illustrate the preparation of pharmaceutical products containing potassium rhodizonate as obtained above, as the active ingredient.

EXAMPLE 3.

Dipotassium rhodizonate (2.50 kilograms), lactose (7.47 kilograms), cornstarch (3.48 kilograms) and magnesium stearate (2.10 kilograms) are mixed together and slugged. The slugs are crushed and passed through a 30 mesh screen. The resulting granules are mixed with magnesium stearate (2.45 kilograms) and tableted in the usual way to give 100,000 tablets. Each tablet weighing 180 milligrams contains 25.0 milligrams of the active ingredient.

EXAMPLE 4.

Dipotassium rhodizonate (10.00 kilograms) and lactose (20.00 kilograms) are mixed, granulated with a 10% acacia solution and dried. The granulate is forced through a 16 mesh screen and, thereafter, mixed with sodium lauryl sulfate (0.20 kilogram), magnesium stearate (1.00 kilogram) and potato starch (8.80 kilograms). The resultant mixture is tableted in the usual way to give 100,000 tablets. Each tablet weighing 40 milligrams contains 20.0 milligrams of the active ingredient.

EXAMPLE 5.

Dipotassium rhodizonate (125 grams) is dissolved in physiological saline solution to make 10 litres and filtered. The resultant solution is filled into 5,000 ampoules under nitrogen atmosphere and the ampoules are sterilized at 115° C for 30 minutes. Each ampoule (2 millilitres) contains 25.0 milligrams of the active ingredient.

WHAT WE CLAIM IS:—

1. A process for preparing dipotassium rhodizonate which comprises polycondensing glyoxal oxidatively in the presence of a potassium salt of carbonic acid and a potassium salt of sulfurous acid.

2. A process as claimed in claim 1, wherein the condensation is carried out at a pH of from 7.5 to 9.0.

3. A process as claimed in claim 1 or claim 2 wherein the glyoxal is condensed in the presence of potassium cyanide as catalyst.

4. A process for preparing dipotassium rhodizonate substantially as described herein, with reference to the foregoing Examples 1 and 2.

5. Dipotassium rhodizonate when prepared by the process claimed in any one of claims 1 to 4.

6. A pharmaceutical composition comprising dipotassium rhodizonate as claimed in claim 5, as active ingredient, together with a solid pharmaceutical carrier.

7. A composition as claimed in claim 6, wherein the carrier is one or more of gum tragacanth, acacia, corn starch, gelatin, potato starch, alginic acid, stearic acid, magnesium stearate or talc.

8. A pharmaceutical composition comprising dipotassium rhodizonate as claimed in claim 5, as active ingredient, together with a liquid pharmaceutical carrier.

9. A composition as claimed in claim 8, wherein the carrier is aqueous sugar or sorbitol or a mixture thereof.

10. A pharmaceutical composition comprising dipotassium rhodizonate as claimed

in claim 5, as active ingredient, the composition being in the form of tablets, capsules, pills a suspension or a solution.

11. A method of treating diabetic diseases in animals other than homo sapiens which comprises the dosage administration of a pharmaceutical preparation comprising dipotassium rhodizonate as claimed in claim 5, as an active ingredient.

12. A pharmaceutical composition comprising dipotassium rhodizonate as claimed in claim 5, as active ingredient substantially as described herein with reference to the foregoing Examples 3, 4 and 5.

SHIONOGI & CO., LTD.,
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1 SHEET *This drawing is a reproduction of the Original on a reduced scale*